Leaning in to the Power of the Possible: The Crucial Role of Women Scientists on Preventing *Haemophilus influenzae* Type b Disease

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**Abstract:** Beginning in an era when female scientists were a lonely minority, women have made major contributions to our understanding of *Haemophilus influenzae* type b (*Hib*) as a pathogen, its treatment and its prevention. The individual scientific and public health contributions, and their collective impact, are reviewed in the context of the development and successful implementation of highly efficacious *Hib* vaccines that are now being deployed to nearly every country worldwide for the prevention of life-threatening pediatric *Hib* disease.

**Key Words:** *Haemophilus influenzae* type b, vaccine, disease control, women

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In the late 19th century, a nutritionally fastidious Gram-negative bacillus was isolated from influenza patients by Pfeiffer and for several decades bore his name (*Pfeiffer’s bacillus*). Its frequent isolation from patients ill or dying from respiratory disease in the 1918 influenza pandemic reinforced its incorrect acceptance as the etiologic agent of that global catastrophe and resulted in its renaming as *Bacillus influenzae*, which was further renamed *Haemophilus influenzae* (*Hi*) by C.E.A. Winslow’s 1920 Committee of Nomenclature of the American Association of Bacteriologists. During this time Anna Wessels Williams, MD (b. 1863 to d. 1954), a close colleague of William H. Park, was one of those directly doubting that this bacterium was indeed the cause of the influenza epidemic noting in 1919 that, “This evidence of multiple strains seems to be absolutely against the influenza bacillus being the cause of the pandemic. It appears to us impossible that we should miss the epidemic strain in so many cases while obtaining some other strain so abundantly. The influenza bacilli, like the streptococci and pneumococci, are in all probability merely very important secondary invaders.” In her diary, Anna Williams also records that “more and more, evidence points to a filterable virus being the cause.”

Even after a “filterable virus” was indeed shown to be the primary agent of human influenza disease in 1933 and the bacillus to be a secondary opportunistic invader, the name *Hi* persisted.

The isolation of the bacillus from the cerebrospinal fluid (CSF) in meningitis had been reported in 1899, and over succeeding decades, it was increasingly recognized that the bacillus could be a primary invasive pathogen, causing sepsis, pneumonia, epiglottitis, arthritis and cellulitis as well as meningitis, particularly in young children. Among scientists in the 1920s, however, there was disagreement about its pathogenicity, which was complicated by observations that Gram-negative bacilli corresponding nutritionally to *Hi* could frequently be isolated from the nasopharynx of healthy children, its microscopic and colonial morphology differed among isolates and it was not consistently virulent in laboratory animals.

Some authors, however, had reported that colonies of *Hi* isolated from the CSF appeared more opaque than throat isolates, and one author reported that *CSF* isolates of *Hi* appeared iridescent.

Soon thereafter began what is nearing a century-long era of substantial advances in the understanding of the biology, pathogenesis, clinical characteristics, treatment and ultimately highly effective preventive vaccination against *Hi* type b (*Hib*), throughout which women scientists have played a pivotal role. Many of these earliest scientific advances were made at a time when women in science were in the minority, making their contributions all the more remarkable. It is through this lens that we chart the substantial advancements made throughout the past century leading to the current state of *Hib* control now achieved or in sight throughout the world.

In 1931 a substantial clarification regarding the nature of the *Hi* organism was made by Margaret Pittman, PhD (b. 1901 to d. 1994) while working at the Rockefeller Institute. She noted that isolates from the throats of healthy individuals were microscopically pleomorphic and formed translucent colonies (which she designated R), while *Hi* freshly isolated from CSF or blood were consistently rod-like and formed larger, iridescent colonies designated S). She further noted that these S colonies upon subculturing often gave rise to R colonies and that the reverse was also true: far as S colonies could be recovered from R cultures by selective methods; that is, the disparate forms of *Hi* were in fact variants of the same species. Although *Hi* isolates had not been meaningfully classified by serologic reactions, Pittman showed that *S* cultures produced a “specific soluble substance” that was precipitated with homologous S antisera, and thus she classified *S* isolates of *Hi* into 2 antigenic types, a and b; the latter was isolated from all the *Hi* strains she studied that were from meningitis cases. After documenting these findings in one definitive article, Pittman moved on to study other pathogens including pertussis, typhoid and cholera. Although reported in a single article, her careful work provided the insight and techniques whereby *Hi* was soon shown to be subclassified into nontypable and typable strains, the latter comprising 6 serotypes determined by capsular antigens, 1 of which, type b (*Hib*), was a major cause of life-threatening disease among infants and children.

With the benefit of Pittman’s findings, Joyce Wright, BM, BCH (b. 1903 or 1904 to d. 1991) made definitive contributions to the mechanism of human immunity to *Hib*. Working with Harvard University colleagues Hugh Ward and Leroy Fothergill, she showed that capsular antibody and complement were bactericidal and that the peak incidence of *Hib* meningitis in infancy correlated with the lack of bactericidal antibody. A graph documenting this inverse relation is among the most highly reproduced in the bacteriologic literature and is likewise reproduced here (Fig. 1).

Through the early 1930s, *Hib* meningitis was almost always fatal (>90% case fatality ratio overall and 97% in infancy).
Wright-Ward-Fothergill group tried energetically to treat the infection with horse antiserum, but with minimal benefit: in a series of 220 treated patients only 31 survived (84% mortality). Successful treatment using passive immunotherapy was achieved by Columbia University pediatrician Hattie Alexander, MD (b. 1901 to d. 1968). By 1939, she developed rabbit antiserum that reduced the mortality to about 20%, and when she combined antiserum with sulfonamides, efficacy was even better. Working with Grace Leidy and Michael Heidelberger, she proved that capsular antibody was the curative component in antiserum, devised methods for its calibration, and showed that the capsular antigen was a phosphate-containing polysaccharide. As antibiotics became clinically available in the 1940s, Alexander carefully compared and found that the drugs were equally efficacious as antiserum in preventing death. The use of antiserum in therapy was discontinued due to cost and the hazard of serum sickness.

In the 1950–1960s, the success of antibiotics had brought the view that bacterial infections were a past problem. Clinicians began to note, however, that the mortality of treated Hib meningitis persisted at 5–10%, due in many cases to the insidious onset of infection causing treatment delay. Vanderbilt pediatrician Sarah Sell, MD (b. 1913 to d. 1968) was influential in documenting that Hib meningitis was not the only objective; she made clear, what many pediatricians knew through their practices, that 30–50% of survivors had clinically significant neurologic sequelae. Working with Grace Leidy and Michael Heidelberger, she proved that capsular antibody was the curative component in antiserum, devised methods for its calibration, and showed that the capsular antigen was a phosphate-containing polysaccharide. As antibiotics became clinically available in the 1940s, Alexander carefully compared and found that the drugs were equally efficacious as antiserum in preventing death. The use of antiserum in therapy was discontinued due to cost and the hazard of serum sickness.

By this time, several academic and pharmaceutical groups had experimented with active immunization with Hib capsular polysaccharide (PS). Maturation of the human antibody response to pure polysaccharides is slow in general, and it was shown that the response to Hib was among the slower to develop from infancy through the 6th year of life. Thus, there was concern that Hib meningitis was most prevalent. Interestingly, however, it had been shown that response to the meningococcus group A (MnA) polysaccharide was appreciable in the first months of life. Coincidentally, a MnA epidemic was ongoing in Finland during the 1970s and early 1980s. Public health physician-scientist P. Helena Makela, MD, PhD (b. 1930 to d. 2011) first organized a successful trial of MnA polysaccharide vaccine in military recruits, with unimmunized subjects serving as controls. Noting that MnA epidemics also affected children, she undertook a controlled efficacy trial of MnA vaccine among children 3–60 months of age and used Hib-PS as the control product because it was similar pharmacologically, visually and in dosage range to the MnA vaccine. Thus Hib-PS vaccine efficacy was an opportunistic, not intentional, objective of the trial and yet this became a seminal Hib vaccine trial. While the MnA vaccine was efficacious even in the youngest children, the Hib vaccine was found to be efficacious only among those administered vaccine at 18 months of age or older. The latter result was welcomed as a means of preventing about a quarter of the cases of Hib meningitis and a larger proportion of Hib epiglottitis cases, as this syndrome has an older age incidence than meningitis. Moreover, Makela's group, which included immunologist Helena Kayhty, PhD (b. 1949) showed that efficacy against Hib disease was correlated with the serum antibody responses, establishing a serologic correlate of vaccine-induced immunity that would eventually be central in the development of vaccines more immunogenic among the youngest age strata and in their licensure. When Hib polysaccharide-protein conjugate vaccines (Hib-CV) were first developed, Makela and Kayhty were involved in their early evaluations in Finland and later worldwide. Further along in the evaluation of Hib-CV, Makela led the study that first identified the capacity of these products to protect vaccinated children against the acquisition of Hib in the oropharynx; this is the biologic basis for the herd effects that feature so prominently in the public health impact of Hib-CV.

Israeli pediatrician Rachel Schneerson, MD (b. 1934), working with collaborators at the US National Institutes of Health, was lead author in the 1971 article that first reported immunogenicity induced by Hib polysaccharide from natural and vaccine exposure and in the 1980 publication first describing a Hib-CV construct. Their synthetic scheme for conjugating Hib polysaccharide to a protein carrier was adopted to make the first commercialized Hib-CV
vaccine (PRP-D). She was recognized for these transformative contributions as a coreipient of the Lasker Clinical Award and Pasteur Award in 1996. During her subsequent career, she has continued to develop vaccines against typhoid and candidate vaccines against several other encapsulated bacteria, tuberculosis and malaria.

With the US licensure of Hib-PS vaccine (April 1985) and then Hib-CV (December 1987) for use in children, the public health community had new powerful tools for Hib disease prevention beyond rifampin and chloramphenicol contact prophylaxis. Claire V. Broome, MD (b. 1949) served in leadership roles at the US Centers for Disease Control (1981–2006) during this transformative time in Hib disease control. She played leading roles in the identification of daycare attendance, a relatively new social phenomenon, as a major risk factor for Hib disease,28 the evaluation and formulation of Centers for Disease Control and Prevention policies on chemoprophylaxis to prevent secondary Hib cases, cost-effectiveness analyses of Hib-PRP vaccine,24 which accelerated the licensure and recommendations for routine use, and policies on use of novel Hib conjugate vaccine products. These contributions included leading case-control effectiveness studies showing that Hib-PS vaccine was insufficiently effective to control the disease,25 establishing population-based surveillance to track the impact of Hib vaccine and demonstrate herd immunity26 and serving as the chair of the Steering Committee for the first ever “vaccine-probe” study of Hib conjugate vaccine. That study revealed the contribution of this organism to all-cause pneumonia in the developing world and the role of the vaccine in preventing associated morbidity and mortality.27 Broome also served as the chair of the Encapsulated Bacteria Committee which reported to WHO’s Strategic Advisory Group of Experts (SAGE) on Immunization and as a member of SAGE when the first global recommendation for use of Hib-CV were issued, paving the way for widespread use throughout the developing world to control morbidity and mortality from Hib.

The US Food and Drug Administration licensure pathway for Hib conjugate vaccines in infants was led by Carolyn Hard-egree, MD, (b. 1984). The first Hib conjugate vaccine (PRP-D) was licensed in 1987 for use only among children 15 months of age and older based largely on comparative immunogenicity data with the existing licensed Hib polysaccharide vaccine, for which efficacy trials had shown prevention of invasive Hib disease in toddlers and older children.22 There was considerable interest from manufacturers to license PRP-D or alternative Hib conjugate vaccine products for use in infants based on immunogenicity studies alone rather than efficacy trials. Dr. Hardegree was unwavering in the view that efficacy trials in infants would be needed for Food and Drug Administration licensure for infant use. Indeed, when the first such trial in the United States23 surprised the vaccine community by failing to confirm the efficacy that had been shown among Finnish infants,30 her tough insistence was vindicated and viewed as highly strategic because disease outcome efficacy trials of other Hib conjugate vaccine products in infants were already underway assuring that the world did not have to wait for these to be initiated.31,32 The introduction of Hib-CV into the Finnish (1987) and then the United States (1987 for use in children 15 months and older and 1990 for use in infants) routine immunization schedule was followed by similar policy decisions in many other developed countries. In 1992, the United Kingdom implemented an infant Hib-CV policy using an abbreviated dosing schedule (ie, without a booster dose). Elizabeth Miller, MB BS (b. 1944), and Mary Ramsay, MB BS (b. 1961), at the UK Health Protection Agency led studies to optimize the disease impact of a Hib-CV program, revealing the importance of a Hib-CV dose in the second year of life to maintain both direct and indirect vaccine impact,31 a dose the United Kingdom had decided to forego at the outset of their program based largely on immunogenicity evidence.

Successful control of Hib disease in the developed world was firmly contrasted by the lack of progress on Hib vaccine uptake in the developing world, where >90% of Hib related deaths were occurring. After several efforts to accelerate country decision making and financing of Hib-CV (ie, the poorest countries of the world were offered free vaccine), rapid progress was only made with the coordinated confluence of several factors: reliable, predictable long-term funding and vaccine pricing for poor countries through the Global Alliance on Vaccines and Immunization, an unambiguous World Health Organization position statement on the recommendation for Hib vaccine use in all countries,33 and the creation by the Global Alliance on Vaccines and Immunization of an international project team, the Hib Initiative (2005–2010), whose aim was to accelerate decision making for Hib-CV implementation by the world’s 72 poorest countries. The Hib Initiative director, Rana Hajjeh, MD (b. 1964), coordinated a team from Johns Hopkins Bloomberg School of Public Health, London School of Hygiene and Tropical Medicine, the Centers for Disease Control and Prevention and the World Health Organization, whose work has resulted in all GAVI-eligible countries committing to Hib vaccine implementation, allowing those with least access to curative therapy and preventive vaccines access to this lifesaving vaccine.34 The last of the now 73 (with the formation of South Sudan) Global Alliance on Vaccines and Immunization-eligible countries is expected to introduce Hib-CV in 2014.

With Hib-CV vaccines now in use in 91% of World Health Organization member countries, we are at a notable milestone in the prevention of Hib disease. Thousands have worked tirelessly in this century-long effort, and it is noteworthy that some of the earlier watershed contributions were made by women scientists working in settings where a remarkable resolve and self-confidence was needed. It is on the shoulders of these pioneers that contemporary women scientists at the bench, the bedside, the field and the conference table, have propelled the Hib prevention goal through the full trajectory of basic biology, epidemiologic characterization, treatment, vaccine development, evaluation, licensure and implementation. There are many other women scientists who have made major contributions to Hib disease control including Claire-Ann Seigrist, Trudy Murphy, Aino Takala, Janet Mohle-Boetani, Mary Slack, Dace Madore, Rosanna Lagos, Kathy Edwards, Catherine Ferraci and Maria Hortal among others. The measure of their collective contributions, along with countless other scientists, clinicians and public health professionals, male and female, is in hundreds of thousands of annual deaths averted, even in the most remote parts of the world. This is a story to celebrate the contributions of these many women who led the way, targeting Hib, tackling it through scientific achievement and perseverance, innovating a novel vaccine and in so doing, moving the needle toward justice and equity in health for children wherever they are born.

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REFERENCES
